Multisensory Processing in Children With Autism: High-Density Electrical Mapping of Auditory–Somatosensory Integration

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Successful integration of signals from the various sensory systems is crucial for normal sensory–perceptual functioning, allowing for the perception of coherent objects rather than a disconnected cluster of fragmented features. Several prominent theories of autism suggest that automatic integration is impaired in this population, but there have been few empirical tests of this thesis. A standard electrophysiological metric of multisensory integration (MSI) was used to test the integrity of auditory–somatosensory integration in children with autism (N = 17, aged 6–16 years), compared to age- and IQ-matched typically developing (TD) children. High-density electrophysiology was recorded while participants were presented with either auditory or somatosensory stimuli alone (unisensory conditions), or as a combined auditory–somatosensory stimulus (multisensory condition), in randomized order. Participants watched a silent movie during testing, ignoring concurrent stimulation. Significant differences between neural responses to the multisensory auditory–somatosensory stimulus and the unisensory stimuli (the sum of the responses to the auditory and somatosensory stimuli when presented alone) served as the dependent measure. The data revealed group differences in the integration of auditory and somatosensory information that appeared at around 175 ms, and were characterized by the presence of MSI for the TD but not the autism spectrum disorder (ASD) children. Overall, MSI was less extensive in the ASD group. These findings are discussed within the framework of current knowledge of MSI in typical development as well as in relation to theories of ASD.

Keywords: autism spectrum disorders; electrophysiology; multisensory integration; auditory processing; somatosensory processing; development

Introduction

Anecdotal reports from parents, clinicians and individuals with autism have lead to the impression that there are significant sensory processing atypicalities in a large percentage of individuals with an autism spectrum disorder (ASD) [Cesarini & Garber, 1991; Grandin, 1992; O'Neill & Jones, 1997; Williams, 1994]. In the 1970’s, sensory processing research was central to the field of ASD, with researchers finding evidence for atypical sensory modulation [e.g. Stroh & Buick, 1964], a preferential reliance on proximal rather than distal senses [Hermelin & O’Conner, 1970], a dominance of somatosensory over auditory stimuli [Hermelin & O’Conner, 1970], a tendency to be overselective in responding to only one aspect of a multisensory object [e.g. Lovaas & Schreibman, 1971; Lovaas, Schreibman, Koegal, & Rehm, 1971], and a tendency to benefit less from visual cues in a visual-motor task than typically developing (TD) children [Hermelin & O’Conner, 1970]. Despite these findings, the research on sensory processing in ASD fell off in the 1980’s and 1990’s, to be replaced by research on higher-order processes, such as executive function [e.g. Ozonoff & Strayer, 1997], language [e.g. Tager-Flusberg, 1996], and social difficulties [e.g. Klin et al., 1999; Tager-Flusberg & Sullivan, 1994], that are also common among persons with ASDs. However, a paradigm shift that once again emphasizes basic sensory processing differences among persons with ASD has emerged in recent years, as evidenced by a resurgence of research utilizing questionnaire methods to describe sensory processing difficulties [e.g. Crane, Goddard, & Pring, 2009; Lane, Young, Baker, & Angley, 2010; Schoen, Miller, Brett-Green, & Nielsen, 2009; Tomchek, 2007], and an emerging literature on unisensory detection and discrimination in ASD [e.g. Bertone, Mottron, Jelenic, & Faubert, 2003, 2005; Bonnel et al., 2003; O’Riordan, 2004; O’Riordan & Plaisted, 2001; O’Riordan & Passetti, 2006]. This shift is particularly evident in the impending changes in the diagnosis of ASD expected in the DSM-V, in which social...
and communication difficulties are being combined into one diagnostic criterion, thus placing equal weight on both the negative (language, socialization, and communication) and positive symptoms (repetitive behaviors, restricted interests, and sensory issues) of autism.

One suggestion that has gained prominence in the autism community, but that has only recently become the subject of empirical investigation, is that a problem with the integration of sensory information may underlie some of the symptoms observed in autism, including the observed sensory hyper- and hypo-sensitivities. Despite renewed interest in sensory issues and the prominence of so-called sensory integration treatment centers and books written on this topic [e.g. Ayers, 1994], surprisingly little empirical work has been conducted to actually test the integrity of multisensory integration (MSI) in autism.

**MSI in Typical Development**

In adults, redundant or mutually informative multisensory inputs tend to be effortlessly integrated, and often lead to faster and better performance on discrimination and detection tasks relative to performance on their unisensory counterparts [e.g. Frens & Van Opstal, 1995; Molholm et al., 2002; Molholm, Ritter, Javitt, & Foxe, 2004; Murray et al., 2005; Perrott, Saberi, Brown, & Strybel, 1990; Spence & Driver, 1997; Stein & Meredith, 1990; Zahn, Abel, & Dell’Osso, 1978]. The same is the case for more complex perceptual-cognitive processes, with faster identification of objects when multisensory inputs are provided and better speech recognition when the speaker’s articulations can be seen compared to when they cannot [Driver, 1996; Molholm et al., 2004; Ross, St-Amour, Leavitt, Javitt, & Foxe, 2007]. The ability to recognize lawful relationships between multisensory inputs is seen from a very early age, with infants able to recognize that audiovisual stimuli are temporally asynchronous as early as 4 months of age [Lewkowicz, 2002]. Natural “sensory deprivation” in humans in cases of early blindness [Hötting, Rösler, & Röder, 2004; Putzar, Goerendt, Lange, Rösler, & Röder, 2007], and controlled sensory deprivation studies in animals [Carriere et al., 2007; Wallace, Perrault, Hairston, & Stein, 2004] reveal that, as might be expected, post-natal interaction with the environment plays a significant role in the development of MSI. Developmental studies also reveal that for some types of information, MSI processes tune-up to optimal levels over the first decade or two of life [Brandwein et al., accepted; Gori, Del Viva, Sandini, & Burr, 2008; Nardini, Jones, Bedford, & Braddick, 2008].

**MSI in ASDs**

While it has been speculated that multisensory processing is impaired in autism, there has been little empirical testing of this notion [see Foxe & Molholm, 2009]. What studies there are have all examined interactions between auditory and visual sensory inputs, and these studies have yielded equivocal results. For example in one study, temporal asynchrony judgments were impaired compared to matched controls for linguistic stimuli but not for non-linguistic stimuli [Bebko, Weiss, Demark, & Gomez, 2006]. In another, Smith and Bennetto [2007] found that children and adults with ASD were less susceptible to the McGurk illusion, in which the percept of a speech sound is changed by the simultaneous presentation of an incongruous visual speech articulation. This suggests that these auditory and visual speech inputs were not integrated in a typical manner in ASD, a finding receiving additional support from work by de Gelder, Vroomen, and van der Heide [1991] who noted that in spite of normal lip-reading ability, individuals with ASD showed less influence of visual speech on auditory speech perception than mental age matched TD individuals. In contrast, van der Smagt, van Engeland, and Kemner [2007], found that children with ASD were just as susceptible to an audiovisual illusion as were TDs. For both groups, hearing multiple sounds resulted in the illusory perception of multiple flashes when only a single flash was presented [the beep-flash illusion, see Shams, Kamitani, & Shimojo, 2000, 2002].

Cross-sensory priming paradigms, in which a visual stimulus precedes an auditory stimulus and its effects on auditory processing are examined, have demonstrated intact visual modulation of the auditory electrophysiological response among persons with an ASD [Magnee, de Gelder, van Engeland, & Kemner, 2008; Magnee, Oranje, van Engeland, Kahn, & Kemner, 2009]. In these studies a visual stimulus was presented 350–500 ms before the onset of an auditory stimulus (in one case the visual stimulus remained on for the duration of the auditory stimulus and in the other it did not), and suppression of the auditory-N1 response was observed. While these data have been interpreted as evidence for intact early multisensory processing in ASD, Vroomen and Stekelenburg [2009] have convincingly demonstrated that this sort of cross-sensory N1 suppression is due to the predictive properties of the preceding visual stimulus on onset of the upcoming auditory stimulus, and not multisensory processing per se. Hence, preservation of such effects in ASD cannot be taken as evidence for intact multisensory processing.

The literature on multisensory processing in ASD thus far has largely been confined to studies that have required behavioral responses to assess multisensory function [but see Magnee et al., 2008, 2009]. While behavioral measures are certainly valuable, a disadvantage of this approach is that it rests on the assumption that observed differences largely reflect multisensory processing, whereas behavioral differences could well be due to differing interpretation of task instruction or...
differences in how attention is allocated (e.g., superior attentional allocation for one group over the other). In either of these cases, the implications are clearly different. In addition, observed similarities in behavior do not necessarily mean that the underlying brain processes are the same. Electrophysiology provides a metric of multisensory processing at multiple stages of the processing hierarchy, and can be generated in the absence of attentional demands through the use of “passive” paradigms in which there is no task. As a result, the integrity of MSI can be assessed without confounding group differences in attentional allocation or task comprehension.

**Electrophysiology of MSI in Typical Development**

Both passive and active paradigms have been used to assess the electrophysiology of auditory–somatosensory integration in TD adults and children, with consistent findings that MSI occurs at multiple processing stages starting early on (circa 50 ms) in cortical areas that were traditionally considered to be unisensory [e.g., Foxe et al., 2000; Lütkenhöner, Lammertmann, Simões, & Hari, 2002]. In one of the first published electrophysiological studies of MSI in children, Brett-Green, Miller, Gavin, and Davies [2008] examined multisensory processing in children between the ages of 6 and 13 years. Using median nerve stimulation and tones presented alone or together, the authors found three time periods during which multisensory interactions occurred: 60–80 ms over central scalp regions of the hemisphere contralateral to the stimulated side, 110–150 ms in the hemisphere ipsilateral to the side of the stimulation over central-parietal areas, and 180–220 ms over central regions bilaterally. These latencies, though slightly later than those found in adults [e.g., Foxe et al., 2002; Murray et al., 2005; Sperdin, Cappe, Foxe, & Murray, 2009], support the notion that children, like adults, integrate multisensory information during both early and later sensory–perceptual time frames.

In the present study, high-density electrophysiology was used to test the integrity of multisensory processing of auditory and somatosensory information among persons with an ASD. Auditory and somatosensory stimuli were presented in randomized order, either alone or simultaneously, in a passive paradigm in which participants engaged in an unrelated activity (watching a silent video). MSI was indexed by comparing electrophysiological responses to the stimuli when presented alone vs. when presented together [e.g., Berman, 1961; Brett-Green et al., 2008; Foxe et al., 2000, 2002; Giard & Peronnet, 1999; Molholm et al., 2002; Murray et al., 2005; Talsma & Woldorff, 2005; Teder-Sälejärvi, McDonald, DiRusso, & Hillyard, 2002]. This commonly used index of MSI entails summing the responses to the auditory and somatosensory stimuli when presented alone and comparing this “sum” waveform to the response to the auditory and somatosensory stimuli when presented together. Because electrical fields sum linearly at the scalp, any differences between the two responses can then be attributed to the two inputs having interacted when they were presented together.1 Our working hypothesis was that this electrophysiological metric would reveal differences in multisensory processing between individuals with ASD and TD, age- and IQ-matched children. Specifically, we predicted a reduction or absence of MSI in ASD at earlier time points, which we assume to reflect more automatic integrative processes, and a corresponding increase in MSI at later time points (>200 ms) reflecting compensatory and less automatic processing.

**Methods**

**Participants**

Seventeen children with ASD and 17 TD children between the ages of 6 and 16 years participated in this study (see Table 1). In accordance with the Declaration of Helsinki, the parents of all the participants provided a written informed consent, and when appropriate, children provided a written assent. All the procedures and consent forms were approved by the Institutional Review Board of the City College of New York.

Exclusionary criteria for both groups included uncorrected vision problems, a history of seizures, and the use of psychotropic medication. TD children were excluded if they had a history of educational, attentional, psychiatric, or developmental difficulties as assessed by a history questionnaire, and were also excluded if their parents endorsed six items of inattention or hyperactivity on a

| Table 1. Participant Characteristics for the Autism Spectrum Disorder (ASD) and Typically Developing (TD) Groups |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Age             | Verbal IQ       | Performance IQ  | Full-scale IQ   |
| TD              | 10.48(2.92)     | 110.3 (11.83)   | 106.53 (13.35)  | 108.4 (12.65)   |
| ASD             | 10.36 (2.71)    | 102.52(18.1)    | 105.06 (14.24)  | 104.7 (14.58)   |
| P-values         | 0.9             | 0.15            | 0.76            | 0.3             |

Values within parenthesis represent SD.

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1The assumption of linearity no longer holds for task-related processes that would be shared for the two unisensory inputs in an active paradigm, such as when each would result in the recruitment of motor cortex to make a button press response. This is because this process would be doubly represented in the summed response and only represented once in the multisensory response. However, in the present study, we are dealing with a passive paradigm and focusing mainly on the sensory processing time frame, and hence the assumption of linearity is expected to hold, with its violation representing the occurrence of multisensory interactions in the brain.

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DSM-IV behavioral checklist of attention deficit disorder (with and without hyperactivity). Both forms were filled out by parents on the first day of testing. The parents of children with ASD were asked to refrain from giving their children stimulant medication \((n = 2)\) before the testing session.

Diagnoses for 15 of the 17 children with ASD were made using both the Autism Diagnostic Interview-R \([\text{ADI-R}; \text{Lord, Rutter, & LeCouter, 1994}]\) and the Autism Diagnostic Observation Schedule \([\text{ADOS-G}; \text{Lord, Rutter, DiLavore, & Risi, 1999}]\) by a trained administrator. For the remaining two, who were diagnosed with Pervasive Developmental Disorder, Not Otherwise Specified \((\text{PDD-NOS}), \text{ADOS, and ADI, data were not available and diagnosis was made on the basis of the diagnostic criteria outlined in the DSM-IV-TR [\text{APA, 2000}]\). Of the 17 ASD participants, seven had autism, eight had Asperger’s disorder, and two had a PDD-NOS. The children with ASD and the TD children were matched on a one-to-one basis, and within one standard deviation on Full Scale and Performance IQ’s \((\text{FSIQ and PIQ})\) as measured by the Wechsler Abbreviated Test of Intelligence \([\text{Wechsler, 1999}]\), as well as on chronological age. The two groups did not differ significantly on any of the matching measures nor on Verbal IQ (see Table 1). All of the children had IQs in the average to above average range with the exception of one TD and one ASD child with IQ’s in the borderline range.

**Stimuli and Procedure**

Testing was conducted over 2 days. In a first session, participants completed the diagnostic and psychometric evaluation. Event-Related Potential \((\text{ERP})\) recordings were conducted on a second visit in a sound attenuated, dimly lit electrically shielded room. Participants were seated in a comfortable chair and watched a film of their choice without sound during the testing protocol, which was presented in three blocks of 10 min each.

**Somatosensory stimulation.** Somatosensory stimulation consisted of a 128-Hz vibrotactile stimulation presented to the child’s right hand for 30 ms. The stimulation was delivered through a 2-layer Transducer manufactured by Piezo Systems, Inc, which was driven by the soundcard of a PC through an audio cable. The stimulator was held with gaze between the child’s thumb, index, and middle finger, and the child’s hand was covered by a black cloth, as seeing somatosensory stimulation can affect the somatosensory response \([\text{e.g. Taylor-Clarke, Kennett, & Haggard, 2002}]\).

**Auditory stimulation.** Auditory stimulation consisted of a 1000Hz tone presented for 30 ms through a speaker placed on the child’s right side. The somatosensory and auditory stimuli could either be presented alone \(\text{unisensory conditions})\) or simultaneously \(\text{multisensory condition})\) for a total of three stimulus conditions: auditory \((\text{A}: 300 \text{ trials})\), somatosensory \((\text{S}: 300 \text{ trials})\) and multisensory \((\text{AS}: 300 \text{ trials})\), totaling 900 trials. The conditions were presented in a randomized order, with a randomized square-wave distribution of Stimulus Onset Asynchrony’s \((\text{SOAs})\) ranging from 700 to 3,000 ms. This large variance in SOA is an effective way to circumvent issues with anticipatory slow-wave activity \([\text{see Teder-Sälejärvi et al., 2002}]\).

**Measures and analyses.** Sixty-eight-channel scalp EEG was recorded, amplified, and digitized at 512 Hz using BioSemi Systems Active Amplifiers. BioSemi uses two electrodes—the Common Mode Sense \((\text{CMS})\), which is actively recorded, and the Driven Right Leg \((\text{DRL})\), a passive electrode—that together form a feedback loop that represent the reference. The acquisition of the data occurs referenced to the CMS-DRL ground which drives the average potential of the participant \(\text{(i.e. the common mode voltage)\ as close as possible to the AC reference}}\) voltage of the Analog-to-Digital box \(\text{(for a description of the BioSemi active electrode system referencing and grounding conventions, visit www.biosemi.com/faq/cmsdrl.htm)}\).

The continuous raw EEG data were first visually inspected to ensure sufficient data quality across our subject population without regard for group membership \((\text{TD or ASD})\). Based on this initial inspection and preliminary exploratory analyses using preset artifact rejection criteria, it was determined that 160 usable trials per condition could reliably be extracted for the vast majority of subjects and this number was then preset as our target trial count. This strategy was motivated by a wish to equate the number of trials sampled from participants from both populations. Specifically, 160 trials of each of the three conditions, distributed evenly across the three stimulation blocks \((55 \text{ trials from each block})\), were selected by hand from the raw EEG to be included in the individual subject averages, with the restriction that the signal did not exceed the artifact rejection criterion of plus or minus 130 microvolts. Note that in almost all cases, there were considerably more than 160 trials that met these criteria. An exception was made in the case of just one ASD participant for whom we could only identify 80 trials across each of the stimulation types that met these criteria. In turn, we sampled just 80 trials per condition from his matched control participant. It is important to point out that during the hand selection procedure, there was no possibility that the evoked brain responses could be visualized in the raw EEG and the experimenter was blind as to group membership. Accordingly trial selection proceeded in an unbiased manner. A second criterion was applied to selection of trials containing somatosensory stimulation. Trials were only chosen for inclusion in averages for those conditions where the presence of a prominent and typical stimulus-artifact from the somatosensory stimulator could be visualized in the raw EEG.
The latter was done as an assurance that somatosensory stimulation had definitively occurred, which could be verified on greater than 75% of trials. This telltale stimulus-artifact results from skin conduction of the electrical current of the stimulator to the electrodes on the scalp. We took this cautious approach because the lack of such a stimulus-artifact could potentially indicate that the stimulator had not made full contact on those trials where it was not fully evident, and we wanted to protect against any possibility that trials without appropriate stimulation might be included in the averages, although this was likely the case on only a very small minority of trials.

For post-processing, a band-pass filter of 2.4 Hz at 12db/octave–30Hz at 12 db/octave was applied to the continuous data. High-pass filtering was performed to remove any ongoing slow-wave activity remaining in the signal, which would otherwise be doubly represented in the summed unisensory response when assessing MSIs [see Molholm et al., 2002; Teder-Sälejärvi et al., 2002]. Low-pass filtering served to remove high-frequency artifact that resulted from the somatosensory stimulator. The EEG data were epoched into 600 ms segments that included the 100-ms preceding stimulus onset, artifact rejected at ±130 μV, and averaged based on stimulation type using Brain Electric Source Analysis version (www.BESA.de). The data were re-referenced to the average reference for all analyses and figures. For analysis of MSIs, the auditory-alone and somatosensory-alone responses were summed for comparison with the multisensory condition.

**Data Analysis**

Analysis of the data was guided by previous studies that have similarly used electrophysiology to assess MSI of simple auditory and somatosensory stimuli [e.g. Foxe et al., 2000]. These studies have shown a series of multisensory modulations that fall on the major peaks of the auditory–somatosensory response over the first 200ms of processing. To constrain our analyses, we therefore used the average of the grand-mean auditory–somatosensory responses from each of the ASD and TD groups to define the peaks of the multisensory response, and constrained our planned analyses to windows around these peaks. The electrodes tested were selected based on the corresponding scalp distribution of the responses at each of the latencies. This technique allowed us to predefine time windows and scalp regions of analysis, and to do so in a way that did not make reference to the dependent measure. Significant interactions with the factor of group were examined by conducting univariate Repeated Measures ANOVA’s. The results of all the ANOVA’s are based on Greenhouse–Geiser corrections.

**Exploratory Analysis**

In addition to the above conservative approach to data analysis, exploratory “cluster plot” analyses were also performed to fully describe the data. In this approach, t-tests are performed for each data point for each electrode and significance values are plotted for each of these points and displayed in a cluster plot. To reduce the probability of Type-1 errors, significant differences are only considered if a criterion of \( P < 0.05 \) is achieved for at least 10 consecutive time points [Guthrie & Buchwald, 1991]. It should be pointed out that this criterion would exclude any effects that did not last for at least 18 ms, given our digitization rate of 512 Hz. This is a suitable alternative to Bonferroni correction for multiple comparisons, which would increase the likelihood of Type II errors through overcompensation for Type I errors. This analysis has the advantage of providing a snapshot of all significant differences within a single frame, and the potential to reveal unpredicted effects that can then be used as a hypothesis generation tool for future studies.

Using this approach, MSIs for each of the participant groups were examined by comparing the multisensory and the sum response. Using this same approach, each of the auditory and somatosensory unisensory responses were compared across the groups to probe for the possibility of group differences in basic sensory processing.

**Results**

*Unisensory Responses*

The electrophysiological responses to the auditory-alone stimuli (Fig. 1) were highly similar in morphology between the two participant groups. The scalp distribution and timing of the auditory response for both groups, illustrated in Figure 1, represents an amalgam of typical auditory-evoked responses for younger and older children, with major responses both fronto-centrally and at lateral temporal scalp regions [Cepioniene, Rinne & Näätänen, 2002]. This is to be expected from our relatively broad age sample. While the group responses were highly similar, starting at 100 ms the ASD response tended to be smaller in amplitude. This diminution of the response can be clearly seen at the response peaks, over fronto-central scalp at 100 ms and over bilateral temporal scalp regions around 150 ms. The electrophysiological responses to the somatosensory-alone stimuli (Fig. 2) also showed a similar morphology across the groups, but here too responses appeared to be larger for the TD group compared to the ASD group, starting at about 70 ms. Somatosensory responses were the greatest contralateral to the side of stimulation, over left central scalp areas, with positive-going peaks at 53 and 110 ms. This latter peak was more pronounced for the TD than
Figure 1. Auditory ERPs for the typically developing children and the children with an autism spectrum disorder at frontal, central and temporal-parietal electrodes. [Color figure can be viewed online at wileyonlinelibrary.com.]
the ASD group. The responses of both groups evolved into a bilateral positive distribution over frontal areas that showed a positive peak at 200 ms and a negative peak at 300 ms.

**Multisensory Interactions**

For the analysis of multisensory interactions, time bins and electrode locations were selected on the basis of the averaged multisensory response collapsed across the two groups. Inspection of the corresponding topographical map revealed five distinct stable spatio-temporal patterns: The first peaked at 53 ms and had a positive distribution focused over the left temporal scalp. A second pattern peaked at 110 ms and had a positive focus over bilateral temporal scalp and a negative focus over the fronto-central scalp. A third peak was noted at 164 ms, and represented a negative focus over the right temporo-parietal scalp. A fourth peak was positive and present at frontal regions at 190 ms. The final stable spatio-temporal configuration peaked at 273 ms, with a positive bilateral temporo-central focus and a corresponding negative frontal focus. These five peaks constituted the center of the time windows that we used in our a priori analyses, with windows of analysis from 43 to 63, 100 to 125, 154 to 178, 175 to 205, and 255 to 299 ms, respectively. Earlier peaks were fitted with smaller time windows while later peaks were fitted with larger windows, to reflect the general pattern of a broadening of componentry at later time points of the evoked response. Data from six separate scalp regions, corresponding to the five distinct spatio-temporal patterns and their contralateral homologs where applicable, were tested. These corresponded to the frontal

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**Figure 2.** Somatosensory ERPs for the typically developing children and the children with an autism spectrum disorder at frontal, central and temporal-parietal electrodes. [Color figure can be viewed online at wileyonlinelibrary.com.]
(F1, Fz, and F2), fronto-central (FC1, FCz, and FC2), left central (T7, C5, and C3), right central (T8, C6, and C4), left temporal (TP7, CP5, and CP3), and the right temporal (TP8, CP6, and CP4) regions. The regions tested for each of the specific time windows were as follows: left and right temporal regions (TP7, CP5, CP3, T8, CP6, and CP4) were tested for the 43- to 63-ms window, left and right temporal regions (TP7, CP5, CP3, T8, CP6, and CP4), and left and right central regions (T7, C5, C3, T8, C6, and C4) were tested for the 100- to 125-ms window, and left and right temporal regions (TP7, CP5, CP3, T8, CP6, and CP4) were tested for the 154- to 178-ms window, fronto-central (FC1, FCz, and FC2) and frontal regions (F1, Fz, and F2) were tested for the 175- to 205-ms window, and finally, fronto-central (FC1, FCz, and FC2), left and right temporal (TP7, CP5, CP3, T8, CP6, and CP4), and left and right central regions (T7, C5, C3, T8, C6, and C4) and were tested for the 255- to 299-ms window. The multisensory and “sum” ERPs were compared using separate repeated measures ANOVAs for each time bin of analysis on the average referenced data, with the between-subjects factor of condition and the within-subjects factors of condition (summed vs. multisensory) and the corresponding region factors. Waveforms from representative electrodes are presented in Figures 3 and 4 for the TD and ASD groups respectively.

The analysis of data from 43 to 63 ms yielded no main effect of condition or any significant interactions. In the 100- to 125-ms window, there was a main effect of condition (F (1, 32) = 6.121, P = 0.019), providing evidence of MSI. Neither group nor region interacted significantly with condition (Ps > 0.53). In the 154- to 178-ms time window, there was a condition by region interaction (F (1, 32) = 9.91, P = 0.004). This interaction showed that the difference between sum and multisensory responses was greater at the left (F (1, 32) = 5.97, P = 0.02) than at the right temporal regions (F (1, 32) = 4.2, P = 0.049). In the 175- to 205-ms time window, there was a main effect of condition (F (1, 32) = 4.727, P = 0.037) and a condition by group interaction that approached significance (F (1, 32) = 3.43, P = 0.073), which was found in a follow-up analysis to be related to the presence of significant differences between summed and multisensory responses for the TD group (F (1, 32) = 8.11, P = 0.008) but not the ASD group (F (1, 32) = 0.51, P = 0.822). Finally, in the 255- to 299-ms time window, there was a condition by group interaction (F (1, 32) = 4.94, P = 0.033), which in a follow-up analysis was found to be related to the presence of significant differences between the summed and multisensory responses for the TD (F (1, 32) = 5.3, P = 0.028) but not the ASD group (F (1, 32) = 0.717, P = 0.4).

Exploratory Analyses

Unisensory responses. In the exploratory analysis of between-group differences in the processing of unisensory stimuli, the statistical cluster plots comparing the auditory responses revealed four time periods of significant difference between TD and ASD children (see panel A of Fig. 5). A first early difference was apparent around 85 ms over central regions, characterized as a slightly larger P1 response for the group of children with ASD, a second difference around 110 ms over parietal and frontal scalp regions representing a smaller N1 response in the ASD group, a third around 210 ms over more central scalp regions, which seemed to represent an N2 response that was shifted earlier in time for the children with ASD, and a fourth late difference around 350 ms over fronto-central scalp regions, which reflected a larger P3 response for the children with ASD. Turning now to the between-group differences in the somatosensory response (see panel B of Fig. 5), there were differences at about 70 and 100 ms, reflecting the smaller positive-going responses at these latencies in the ASD group over the left centro-parietal regions. A difference was also seen at 150 ms due to a smaller negative going response in the ASD group over the left centro-parietal scalp. Other differences were noted at around 280 ms over the centro-parietal and parietal regions, with the somatosensory response in this time frame appearing to occur earlier for the ASD than the TD group. Finally, late differences were noted again around 380 ms over frontal regions, which reflected a greater response in the ASD compared to the TD group (see panel B of Fig. 5).

Multisensory responses. Exploratory analysis of MSIs using the statistical cluster plots painted a straightforward picture of the MSIs in the ASD and TD groups (see Panels C and D of Fig. 5). Specifically, the plots revealed a pattern of MSI from about 120–200 ms that was present in the TD group but not in the ASD group. This timing encompassed the initial three MSI effects established in our a priori analysis. For the ASD group, a clear pattern of MSI only emerged at about 300 ms (from ~325 to 375 ms), a time frame that was not included in our a priori analysis. In the TD group, there was also evidence for a second MSI effect at about 400 ms. Lowering the criterion to a less restrictive one of five successive significant points failed to reveal any additional clear patterns in the ASD group beyond that at 300 ms, but did serve to solidify the effects at ~120 and 400 ms in the TD group, and also showed short-lived effects that fell into the 250- to 300-ms range that was significant for this group in the ANOVA. There may even be a hint of an earlier effect at about 64 ms in the TD group that would bear replication in a follow-up study.

Discussion

The notion that fundamental differences in MSI are core to ASD has been at the forefront of a number of influential theories of the disorder since its original description by Kanner in the 1940’s. In the present study, the integrity of MSI in children with ASD was...
interrogated with scalp-recorded electrophysiology using a passive auditory–somatosensory stimulation paradigm. On the basis of our primary analyses, it appeared as though both TD and ASD groups were integrating the sensory inputs by 110 ms (as shown in main effects of condition for the 100- to 125-ms and 154- to 178-ms windows of analyses). However, during these time frames, the difference between the multisensory and summed responses were mainly driven by the TD group (see Fig. 5, panels C and D), suggesting that we may not have had the power to detect group interactions in this time frame. For later time periods of analysis, at 175 and 255 ms, there was evidence for integration among the TD but not the ASD participants. A fuller test of our

Figure 3. Multisensory vs. summed ERP waveforms for the typically developing children at frontal, centro-parietal, temporal and temporal-parietal electrodes. [Color figure can be viewed online at wileyonlinelibrary.com.]
data using an exploratory approach corroborated the multisensory effects in the ~100- to 200-ms range in the TD group, whereas in the children with ASD, MSI was only evident starting at about 310 ms. These findings together suggest that among children with ASD, there is a decrease in the extent of the automatic integration of sensory inputs (i.e. MSI) compared to TD children.

We were surprised that the primary analysis failed to reveal MSI before 100 ms in the TD group. In adults, electrophysiological evidence of the integration of

Figure 4. Multisensory vs. summed ERP waveforms for the children with an autism spectrum disorder at frontal, centro-parietal, temporal and temporal-parietal electrodes. [Color figure can be viewed online at wileyonlinelibrary.com.]
auditory and somatosensory inputs is reliably seen between 50 and 70 ms [Foxe et al., 2002; Murray et al., 2005; Sperdin et al., 2009], and the one electrophysiological study of AS integration in children, of a similar age range to the ones tested here, found MSI between 60 and 80 ms [Brett-Green et al., 2008]. Based on our extensive work on MSI in healthy adults [Foxe et al., 2000; Foxe & Schroeder, 2005; Molholm et al., 2002, 2004; Molholm, Martinez, Shpaner, & Foxe, 2007; Murray et al., 2005; Taylor-Clarke et al., 2002], in which such effects are consistently found for AS, AV, and visual-somatosensory pairings, we have suggested that early stages of MSI (circa. 40–90 ms) serve the function of simple coincidence detection, and of response enhancement for near threshold stimuli. Further, that this early tagging of inputs is essential to the binding of information that is processed through different sensory pathways with different transmission times and numbers of relay stations [Foxe & Schroeder, 2005; Schroeder & Foxe, 2005]. It is however possible that these relatively transitory/short-lived effects shift in timing over childhood, and that this rendered our tests, on a sample that spanned a relatively broad range of ages, insensitive to the early effect. We should note that there was a hint of early MSI in the TD group in our “exploratory” analysis of the data, but since this was not shown in our primary analysis and only appears in a small set of electrode sites, this result needs to be replicated in future work. Ongoing work in our laboratory on the developmental trajectory of AS MSI, in which we will examine tighter age groups ranging from 2 to 3 years old.

Figure 5. Panels A and B, represent cluster plots comparing children TD and ASD children with respect to (A) auditory-alone responses, and (B) somatosensory-alone responses. Panels C and D, represent cluster plots of the difference between summed and multisensory responses for the (C) TD and (D) ASD children. Significance is represented here only if there were 10 consecutive time points that differed in the comparisons. The x-axis represents time (in ms). The y-axis represents individual electrode positions. Starting from the bottom of the graph, the electrodes are divided into sections from posterior to anterior scalp. Within a section, the electrodes are arranged from the right most lateral to the left most lateral sites. The sections are labeled based on the midline of the scalp (e.g. “central” includes electrodes over temporal scalp).
The current data indicate that children with ASD do not automatically combine sensory inputs early in the processing hierarchy to the same degree as TD individuals, as assessed by the absence of audio-somatosensory MSIs in the 100- to 200-ms time frame. These findings are in line with several theories of ASD, including the temporal binding hypothesis [Brock, Brown, & Boucher, 2002] and the underconnectivity hypothesis [e.g. Just, Cherkasskyy, Keller, Kana, & Minshew, 2007]. Both of these theories begin from the premise that in ASD there is a tendency to focus on the local rather than the global aspects of information, a thesis that was originally formulated by Frith and Happe [1994] and termed as weak central coherence. According to the temporal binding hypothesis, the local bias in ASD is related to a failure to integrate information from different specialized networks in the brain [Brock et al., 2002]. This failure to integrate information has also received some support from findings of local overconnectivity between proximal areas as evidenced by findings of increased minicolumnar density in postmortem studies [Casanova, 2007] and functional underconnectivity between more distal areas of the brain as evidenced by fMRI [Just, Cherkassy, Keller, & Minshew, 2004]. Findings of both brain under- and over- connectivity [Mizuno, Villalobos, Davies, Dahl, & Müller, 2006] provide a simple physiological basis for proposed differences in multisensory processing in ASD, which would be expected to require distal brain connectivity [e.g. Falchier, Clavagnier, Barone, & Kennedy, 2002; Rockland & Ojima, 2003; Smiley & Falchier, 2009]. Evidence of functional underconnectivity between frontal and visual areas in ASD has been replicated during both rest [Cherkasskyy, Kana, Keller, & Just, 2006] and a variety of experimental tasks that include response inhibition [Kana, Keller, Minshew, & Just, 2007], working memory [Koshino et al., 2005], and executive function [Just et al., 2007]. In addition to findings of underconnectivity, functional overconnectivity between the thalamus, a key relay area in sensory processing, and certain frontal regions that include the left insula and right postcentral and middle frontal gyri has also been noted [Mizuno et al., 2006]. Pathophysiological findings from postmortem tissue of the brains of persons with ASD are also consistent with atypical connectivity. There are reliable differences in relation to the TD brain, with findings of a smaller minicolumnar width, a greater number of minicolumns, and increased neuronal density in various cortical areas including the frontal and temporal lobes [Casanova, 2004, 2006]. Together these findings indicate possible functional and anatomical differences that may contribute to problems with MSI, which requires rapid and accurate communication between subcortical and cortical areas.

Crucially, evidence from anatomical studies have shown that there are direct long range connections between the various sensory cortical areas [Falchier et al., 2002; Rockland & Ojima, 2003] and it may be the disruption of this form of connectivity that leads to impairment of early MSI in ASD.

A major question raised is how to reconcile our findings with the few behavioral studies on multisensory processing in autism that suggest that the integration of basic stimuli is typical in ASD [e.g. Bebko et al., 2006; van der Smagt et al., 2007], whereas it is the integration of more complex stimuli, such as language that is impaired [e.g. Mongillo et al., 2008; Smith & Bennett, 2007]. All these studies have involved auditory–visual stimuli, so one possibility is that the difference lies in the sensory modalities involved. Another possibility is that while individuals with autism are able to benefit from multisensory inputs, especially for simpler stimulus and task configurations, the underlying brain processes nevertheless differ.

It is also possible that for persons with ASD, actively attending the stimuli is necessary for integration to occur. That is, that MSI processes that occur in the absence of directed attention in TD individuals require attention to be achieved in this population. It will be interesting to assess if making the stimuli task-relevant serves to “normalize” the neural responses, or if typical behavioral facilitation is seen in the face of different neural processing.

Another potential contribution to differences in the integration of the auditory and somatosensory stimuli might come from the small but reliable differences in the magnitude of the unisensory responses that were observed between the groups. Although for both groups there were robust unisensory responses which were in the main highly similar between the groups, these appeared slightly smaller in the ASD group. Just how this would impact subsequent processing is difficult to say, but we doubt that the whole-scale differences that we see in multisensory processing would be mitigated by “normalizing” the unisensory response. One possibility is that in ASD multisensory processing is more (or less) mature than for TD individuals. Only by collecting considerably more data points, however, will we be able to paint the developmental trajectory of auditory–somatosensory MSI and address such questions. A number of studies have specifically examined how the “effectiveness” of unisensory stimulation impacts MSI. For studies that record single cell activity, effectiveness is assessed by the number of spikes per unit of time. Such studies have demonstrated that the more ineffective unisensory stimuli are at eliciting a neuronal response when presented alone, the greater the multisensory enhancement tends to be when they are presented together [e.g. Stein & Stanford, 2008; Stein, Stanford, Ramachandran, Perrault, & Rowland,
This is referred to as the “principle of inverse effectiveness”. According to this principle, one could in fact make the case that the unsensory stimuli used here were less effective for the ASD group and therefore that their MSIs should in fact be stronger. The relationship between the robustness of the unsensory response and the magnitude of the multisensory response has not been so straightforward when tested using other methods. For example, some fMRI studies find support for inverse effectiveness [e.g. Werner & Noppeney, 2009], whereas others have actually shown quite the opposite, with enhanced integration seen as the effectiveness of unsensory stimulation increased [Kim & James, 2010]. Behavioral data from our laboratory reveal that for more complex linguistic stimuli, the largest audiovisual multisensory effects are present for stimuli that are at intermediary stages of effectiveness, suggesting that there is not necessarily a linear relationship between the effectiveness of unsensory stimuli and MSI [e.g. Ma, Zhou, Ross, Foxe, & Parra, 2009; Ross et al., 2007]. Clearly much work remains to be done to understand how the differences in unisensory processing relate to differences in multisensory processing.

Conclusions

The findings from this study provide preliminary confirmatory evidence for anecdotal and clinical reports of a difficulty in integrating information from multiple sensory modalities among persons with ASD. Much work, of course, remains to be done to fully understand not only the differences in how multisensory inputs are integrated but also how these differences affect higher-order processing, and the impact that a lack of early integration has on the pathogenesis of persons with ASDs. In addition, it will be important to determine whether there are specific phenotypic characteristics of autism (e.g. sensory overresponsiveness) that are more strongly associated with differences in multisensory processing than others, as well as whether MSI deficits are more strongly associated with specific subtypes of the autism spectrum than others (e.g. autism vs. Asperger's syndrome).

Acknowledgments

Initial support for this work came from a pilot grant from Cure Autism Now (J.J.F.). Additional support came from the US National Institute of Mental Health (MH 085322 to S.M. and J.J.F.) and The Wallace Research Foundation (S.M. and J.J.F.). NR received additional support from a Post Doctoral Research Grant from the Fondation du Québec de Recherche sur la Société et la Culture and from the Autism Research Training Program through the Canadian Institute of Health Research.

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